REMARKS

Claims 1-19, 29-32, 34-37, 41, 42, 44-48, 53-62, 64, 66, and 67, as amended are pending in the application. Claims 20-28, 33, 38-40, 43, 49-52, 63, and 65 are canceled without prejudice. For the most part, the amendments to the claims were made at the request of the Examiner to excise any non-elected subject matter. Support for the amendments is found in the specification. Therefore, no new matter is presented with the amendments.

Requirement of Amendments in Light of Restriction

In the current Office Action, the Examiner points out that the pending claims reading on the elected compounds when W is aryl and T is aryl, i.e. the 4-phenyl-3-arylalkylamino-piperidines are prosecuted and recommended that non-elected scope wherein W and T are not aryl be deleted from the claims. Applicants point out that with the amendments to claims 10, 13, 17, 19, 42, and 46-48 this requirement has been met. In light of these amendments, applicants respectfully request removal of this requirement.

Rejection of Claim 58 Under 35 U.S.C. §112, Second Paragraph

Claim 58 stands rejected under 35 U.S.C. §112, second paragraph as being indefinite for allegedly failing to point out and distinctly claim the subject matter which applicants regard as their invention. The Examiner points out that the claim as originally submitted lacked a dosage limitation. In reply, applicants have amended claim 58 adding the term "therapeutically effective amount." In light of the amendments, applicants request that this rejection be reconsidered and withdrawn.

Rejection of Claim 65 Under 35 U.S.C. §112, Second Paragraph

Claim 65 stands rejected under 35 U.S.C. §112, second paragraph as being indefinite for allegedly failing to point out and distinctly claim the subject matter which applicants regard as their invention. The Examiner objects to the use of the term "providing end organ protection." Without acquiescing to the rejection and in order to facilitate prosecution, applicants have canceled claim 65. Therefore, this rejection is rendered moot.

Rejection of Claims 60-66 Under 35 U.S.C. §112, Second Paragraph

Claims 60-66 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for allegedly failing to point out and distinctly claim the subject matter which applicants regard as their invention. The Examiner objects to the term "preventing" alleging the term is self conflicting since once a disorder or symptom has been diagnosed and the subject is in need of treatment, the de novo "prevention" can not be made. The Examiner further relates that the "prevention" can only be in preventing recurrence of disorder or pathology, i.e. a maintenance dose preventing recurrence of disorder or symptom which is embraced by the term "treatment." With regard to now-canceled claims 63 and 65, this rejection is rendered moot. Regarding claims 60-62, 64, and 66, this rejection is respectfully traversed.

Applicants point out that Applicants agree with the Examiner that a medicine is not arbitrarily administered to healthy patients because of the inherent risks present in almost all drugs, but there are numerous medications that are indicated by the FDA for administration to patients who do not presently manifest the symptoms of a given disease but are indicated to be at risk for incurring or developing said disease. In many of these instances, the FDA authorizes the term "preventing" be used. For example, provided below is the indications portion of the label for Fosamax®, Merck's marketed drug for the treatment and prevention of osteoporosis:

INDICATIONS AND USAGE

FOSAMAX is indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
  - For the treatment of osteoporosis, FOSAMAX increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*.)
  - For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

    Bone loss is particularly rapid in postmenopausal women younger than age 80. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of FOSAMAX for prevention of osteoporosis.

Issued December, 2004 (emphasis added).

http://www.merck.com/product/usa/pi_circulars/f/fosamax/fosamax_pi.pdf

In the context of claim 62, a method of preventing "stroke", the mere fact a patient may be of sufficient age and have the requisite level of hypertension may warrant the administration

of a compound of the present invention to "prevent stroke." The patient has not been diagnosed as having a stroke, yet a renin inhibitor of the present invention may, in the future, be indicated for such a use in such a situation. At this point it is unclear what requirements the FDA may impose. However, the term "prevention" in this context is definitely not self-conflicting. Applicants therefore request that this rejection be reconsidered and withdrawn.

Rejection of Claim 63 Under 35 U.S.C. §112, First Paragraph

Claim 63 stands rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the enablement requirement. The Examiner objects to the claiming of the treatment of myocardial infarction alleging that said condition is an irreversible cardiac injury and cannot therefore be treated. Without acquiescing to the rejection and in order to facilitate prosecution, applicants have canceled claim 63. Therefore, this rejection is rendered moot.

Rejection of Claims 1-19, 27-32, 34-37, 41-48, 51-58 and 67 Under 35 U.S.C. §103 Based on Binggeli et al. (USP 6,051,712) in view of Binggeli et al. CA 126 Structure Delineation

Claims 1-19, 27-32, 34-37, 41-48, 51-58 and 67 stand rejected under 35 U.S.C. §103 based on Binggeli et al. (USP 6,051,712) in view of Binggeli et al. CA 126 Structure Delineation. With regard to now-canceled claims 27-28, 43, and 51-52, this rejection is deemed to be moot. With regard to the pending claims as amended, this rejection is respectfully traversed.

The Examiner relates that Binggeli et al. (USP 6,051,712) generically discloses the claimed compound, process of making said compounds and use of said compounds as renin inhibitors. The Examiner further relates that Bingelli et al. '712 discloses all the elements of the claims except that a particular species wherein X is N was not exemplified. The Binggeli CA reference is cited in support, but does not appear to provide substantively different moieties as it is abstracting the international (WO) equivalent to the Bingelli et al. '712 patent.

In reply, Applicants point out that neither reference, alone or in combination disclose, either generically or specifically, all the elements of the claim. Building on the Examiner's remarks, not only is the particular species wherein X is N not exemplified, it is also not generically disclosed. For example, note that Bingelli's substituent X is defined as a bond, oxygen, sulphur or a group $-CH-R^{11}-$, $-CHOR^{9}-$, -O-CO, -CO- or $C=NOR^{10}-$ with the bond

emanating from an oxygen or sulphur atom joining to saturated C atom of group Z or to R^1, and it is further limited by the provisos at the end of the claim. There is no amine in the definition.

The Examiner's position is impliedly that the moiety X^1 of the R^4 substituent is equivalent to the X moiety of the $-X-[Z]_n-R^1$ substituent and therefore, one that is skilled in the art would have automatically contemplated replacing the X moiety of the $-X-[Z]_n-R^1$ substituent with those groups defined for the X^1 moiety of R^4. If the substituent R^4 were in fact equivalent to the $-X-[Z]_n-R^1$ the Applicant of the B reference would not have specifically defined the substituents R^4 and $-X-[Z]_n-R^1$ differently. In fact there are chemical entities which are included in the definition of R^4 that are not included in the definition for the $-X-[Z]_n-R^1$ substituent and vice versa. For example, R^4 includes an oxo group as a possible substituent while the substituent $-X-[Z]_n-R^1$ does not contemplate this option. Additionally, substituent R^4 contemplates moieties that included sulfonic acid moiety wherein the substituent $-X-[Z]_n-R^1$ does not. Conversely, the substituent $-X-[Z]_n-R^1$ includes in its definition of X a variety of groups which are not included in the definition of X^1 including an imine, sulfur, keto, and ester, for example. Given that Binggeli et al. specifically define the substituents R^4 and $-X-[Z]_n-R^1$ differently, they obviously intended that the substituents at the 3 and 5 position of the piperidine ring were not equivalent. Given this, the skilled person in the art would not automatically have contemplated replacing the X moiety of the $-X-[Z]_n-R^1$ substituent with those groups defined for the X^1 moiety of R^4. Furthermore, there is no teaching or suggestion by Binggeli et al. that the X moiety of the $-X-[Z]_n-R^1$ substituent and the X^1 moiety of R^4 are interchangeable or equivalent.

Applicants also point out that one of ordinary skill in the art would not view the amine, NR^{11}, included in the definition for the X^1 moiety of R^4 as equivalent to many of the subtituents which define the X moiety of the $-X-[Z]_n-R^1$ substituent. For example, an amine is not equivalent to a bond or an imino, ether, ester, or keto moiety in terms of a variety of chemical properties including sterics, electronics, and acidity/basicity. The reactivity of an amine can differ greatly than that of a imino, ether, ester, or keto moiety especially when one considers the variety of groups which can be bonded to these moieties as are defined by Z^1 and Z.

Furthermore, the skilled person in the art would not automatically contemplate replacing the X moiety of the $-X-[Z]_n-R^1$ substituent with those groups defined for the X^1 moiety of R^4 due to the fact that the compounds of Formula I have at least 2 asymmetric carbon atoms. The Examples and Schemes of Binggeli et al. describe compounds of Formula 1 where the relative

configuration of the two substituents of the 3- and 4-positions of the piperidine ring is trans. Given the importance of the trans relative configuration as is evidenced by the Schemes and Examples disclosed, one that is skilled in the art would not expect to simply replace the X moiety of the $-X-[Z]_n-R^1$ substituent with those groups defined for the X^1 moiety of R^4 and ultimately produce the compounds disclosed in Binggeli et al. based on the synthetic methodologies and relative configuration described therein. These stereochemical differences further support the notion that Binggeli et al. did not contemplate that the X moiety of the $-X-[Z]_n-R^1$ substituent is equivalent to, or could be replaced with, those groups defined for the X^1 moiety of R^4 and therefore, defined X^1 and X differently and uniquely.

Binggeli et al. CA 126 Structure Delineation does nothing to remedy the deficiencies of Binggeli et al. '712 since it is merely abstracting the international equivalent to the Binggeli et al. '712 patent. There is no teaching or suggestion of applicants compounds containing an amine at the X substituent of the Binggeli compounds further configured so that the two substituents of the 3- and 4-positions of the piperidine ring are in the cis configuration.

Since both references fail to teach or suggest the claimed invention for the same reasons, they are also deficient for the same reasons when used in combination. Therefore, applicants respectfully request that the rejection of the pending claims under 35 U.S.C. §103 based on the disclosures of the Bingelli et al. '712 patent in view of Bingelli et al. CA 126 Structure Delineation be reconsidered and withdrawn.

CONCLUSION

In light of the amendments and arguments made above, applicants respectfully request reconsideration withdrawal of the pending rejections and that this case be allowed. A prompt and favorable notice to that effect is earnestly solicited.

Respectfully submitted,

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